(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 919 218 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
02.06.1999 Bulletin 1999/22

(21) Application number: **98907242.6**

(22) Date of filing: **16.03.1998**

(51) Int. Cl.[6]: **A61K 7/00**, A61K 7/48, A61K 35/78

(86) International application number:
PCT/JP98/01095

(87) International publication number:
WO 98/41183 (24.09.1998 Gazette 1998/38)

(84) Designated Contracting States:
DE FR GB IT

(30) Priority: **19.03.1997 JP 85746/97**

(71) Applicant:
SHISEIDO COMPANY LIMITED
Chuo-ku, Tokyo 104-8010 (JP)

(72) Inventors:
- **YAGI, Eiichiro,**
  Shiseido Res. Cnt
  Shiseido co. Ltd
  Kanagawa 223-8553 (JP)
- **SUZUKI, Rikako,**
  Shiseido Res. Cnt
  Shiseido co. Ltd
  Kanagawa 223-8553 (JP)
- **NAGANUMA, Masako,**
  Shiseido Res Cnt
  Shiseido Co Ltd
  Kanagawa 223-8553 (JP)
- **OHTA, Masahiro,**
  Shiseido Res Cnt
  Shiseido co. Ltd.
  Kanagawa 223-8553 (JP)

(74) Representative:
TER MEER STEINMEISTER & PARTNER GbR
Mauerkircherstrasse 45
81679 München (DE)

(54) DERMATOLOGIC PREPARATIONS FOR BEAUTIFYING

(57) A whitening endermic liniment which characteristically contains an extract from a plant of the Solanaceae family, genus Solanum, an extract from a plant of the Fabaceae family, genus Gliricidia, or an extract from a plant of the Asteraceae family, genus Brickellia.

The present invention can provide a whitening endermic liniment which exhibits superior whitening effects and hypochromic effects on pigment deposition, chloasma, freckles, liver spots, etc. after sun exposure and is superior in terms of safety.

EP 0 919 218 A1

Description

FIELD OF THE INVENTION

[0001] This invention relates to a whitening endermic liniment which, because it contains an extract from a plant of the Solanaceae family, genus Solanum, suppresses production of melanin and is effective in the prevention of and improvement in pigment deposition, chloasma, freckles, liver spots, etc. after sun exposure.

[0002] This invention also relates to a whitening endermic liniment which, because it contains an extract from a plant of the Fabaceae family, genus Gliricidia, suppresses production of melanin and is effective in the prevention of and improvement in pigment deposition, chloasma, freckles, liver spots, etc. after sun exposure.

[0003] This invention also relates to a whitening endermic liniment which, because it contains an extract from a plant of the Asteraceae family, genus Brickellia, suppresses production of melanin and is effective in the prevention of and improvement in pigment deposition, chloasma, freckles, liver spots, etc. after sun exposure.

BACKGROUND OF THE INVENTION

[0004] The mechanism of the development of chloasma and such on skin, although there are some unknown details, is generally believed to result from the formation of melanin pigment due to hormonal abnormalities or ultraviolet light stimulation from sunlight followed by abnormal deposition of this pigment in the skin.

[0005] This melanin pigment which causes the coloring of the skin is produced in melanin producing granules (melanosomes) in melanin cells (melanocytes) between the epidermis and the corium. Melanin thus produced is then diffused to neighboring cells by means of osmosis. The biochemical reactions in the melanocytes are speculated to be those described below.

[0006] That is, the production process of melanin pigment is thought to be as follows: tyrosine, one of the essential amino acids, becomes dopaquinone through the action of the enzyme tyrosinase, and this is then changed to a red pigment, to a colorless pigment and finally to melanin, which is black, by enzymatic as well as non-enzymatic oxidation.

[0007] Therefore, in order to suppress the production of melanin, it is important to suppress the first stage of the reactions, i.e. the action of tyrosinase.

[0008] However, compounds which suppress tyrosinase action, with the exception of hydroquinone, work very slowly and do not give sufficient improvement in pigment deposition in the skin.

[0009] On the other hand, hydroquinone, although its effects are recognized, has the problem of sensitization and therefore its uses are generally limited. For the purpose of improving its safety, attempts have been made to modify it into a monoester of a higher fatty acid, an alkyl monoether and such (Japanese unexamined patent publication Tokkai Sho 58-154507). However, esters are decomposed by hydrolytic enzymes in the body and therefore are not necessarily safe. Sufficiently safe ethers have not been obtained yet either.

[0010] For the purpose of solving these problems, the inventors investigated a wide variety of substances for a melanin production suppression effect, and discovered that an extract from a plant of the Solanaceae family, genus Solanum, a plant of the Fabaceae family, genus Gliricidia, or a plant of the Asteraceae family, genus Brickellia, had melanin production suppression and tyrosinase inhibition actions and thus completed the present invention.

[0011] An extract of a plant of the Solanaceae family, genus Solanum, was reported to have been used in an endermic liniment for improvement in the skin with pimples (Japanese unexamined patent publication Tokkai Sho 56-154500). However, applications of this extract in melanin production suppression actions or in whitening agents is not known at all. The inventors completed the present invention based on this finding.

[0012] Extracts from either plants of the Fabaceae family, genus Gliricidia or plants of the Asteraceae family, genus Brickellia, are not known at all for their use in endermic liniments, not to mention in whitening agents.

[0013] The object of the present invention is to provide a whitening endermic liniment which has superior melanin production suppression effect and tyrosinase inhibition effect and is superior in terms of safety.

DISCLOSURE OF THE INVENTION

[0014] That is, the present invention is a whitening endermic liniment which characteristically contains an extract from a plant of the Solanaceae family, genus Solanum.

[0015] Also, the present invention provides said whitening endermic liniment wherein the plant of the Solanaceae family, genus Solanum, is jurubeba paiz (scientific name: Solanum paniculatum).

[0016] Furthermore, the present invention provides said whitening endermic liniment wherein the blend ratio of the extract from the plant of the Solanaceae family, genus Solanum, is 0.0005 - 10.0 wt%.

[0017] Also, the present invention is a whitening endermic liniment which characteristically contains an extract from a plant of the Fabaceae family, genus Gliricidia.

[0018] Furthermore, the present invention provides said whitening endermic liniment wherein the plant of the Fabaceae family, genus Gliricidia, is Cocohuite (scientific name: Gliricidia sepium).

[0019] Also, the present invention provides said whitening endermic liniment wherein the blend ratio of the extract from the plant of the Fabaceae family, genus Gliricidia, is 0.0005 - 10.0 wt% of the total whitening endermic liniment.

[0020] Also, the present invention is a whitening endermic liniment which characteristically contains an extract from a plant of the Asteraceae family, genus Brickellia.

[0021] Furthermore, the present invention provides said whitening endermic liniment wherein the plant of the Asteraceae family, genus Brickellia, is Hamula (scientific name: Brickellia cavanillesy).

[0022] Also, the present invention provides said whitening endermic liniment wherein the blend ratio of the extract from the plant of the Asteraceae family, genus Brickellia, is 0.0005 - 10.0 wt% of the total whitening endermic liniment.

THE BEST MODES OF THE EMBODIMENTS

[0023] The present invention is described in detail below.

[0024] For the plant of the Solanaceae family, genus Solanum, used in the present invention, jurubeba paiz (scientific name: Solanum paniculatum) is preferable. This plant is found on dry grassy plains and pastures particularly in Brazil.

[0025] The melanin production suppression effect and the tyrosinase inhibition effect of the extract of the plant of the Solanaceae family, genus Solanum, was discovered by the inventor for the first time. Its application to whitening agents and whitening endermic liniments is not known at all.

[0026] For the plant of the Fabaceae family, genus Gliricidia, used in the present invention, Cocohuite (scientific name: Gliricidia sepium) is preferable. However, Gliricilia (scientific name: Gliricidia kunph) is also effective and the selection is not limited to Cocohuite. Cocohuite is found on dry grassy plains and pastures particularly in Mexico.

[0027] The melanin production suppression effect and the tyrosinase inhibition effect of the extract of the plant of the Fabaceae family, genus Gliricidia, was discovered by the inventor for the first time. Its application to whitening agents and whitening endermic liniments is not known at all.

[0028] For the plant of the Asteraceae family, genus Brickellia, used in the present invention, Hamula (scientific name: Gliricidia sepium) is preferable. However, Earleaf brickellbush (scientific name: Brickellia amplexicaulis) and Betonyleaf brickellbush (scientific name: Brickellia betonicifolia) are also effective and the selection is not limited to Hamula. Plants of the genus Brickellia are shrubs which grow in warm areas in Mexico and America.

[0029] The melanin production suppression effect and the tyrosinase inhibition effect of the extract of the plant of the Asteraceae family, genus Brickellia, was discovered by the inventor for the first time. Its application to whitening agents and whitening endermic liniments is not known at all.

[0030] The extract used in the present invention is obtained by immersing or heated refluxing of roots, leaves, tubers, stems, fruits, etc. or the whole aforementioned plant in an extraction solvent, followed by filtering and condensation. The extraction solvent used in the present invention can be any solvent which is normally used for extraction. Examples include alcohols such as methanol and ethanol, hydrated alcohols, and organic solvents such as acetone and ethyl acetate, and these can be used either independently or in combination.

[0031] In the present invention, the blend ratio of the extract from the aforementioned plants, in a dry form, is 0.0005 - 10.0 wt%, preferably 0.01 - 5.0 wt%, of the total endermic liniment. If it is less than 0.0005 wt% then the effects of the present invention cannot be sufficiently achieved, and if it is more than 10 wt% then pharmaceutical preparation becomes difficult. Therefore neither case is preferable. No significant increase in the effect is observed when using more than 5 wt%.

[0032] In addition to the essential ingredient described above, the endermic liniment of the present invention can contain, as necessary, those ingredients such as are normally used in cosmetics, drugs, etc. in the form of an endermic liniment, including other whitening agents, humectants, antioxidants, oil-based ingredients, ultraviolet light absorbents, surfactants, thickeners, alcohols, powder ingredients, colorings, water-based ingredients, water and various skin nutrients.

[0033] In addition, sequestering agents including disodium edetate, trisodium edetate, sodium citrate, sodium polyphosphate, sodium metaphosphate and gluconic acid, drugs including caffeine, tannin, verapamil, tranexamic acid and its derivatives, glycyrrhiza extract, glabridin, various crude drugs, tocopherol acetate, glycyrrhizic acid and its derivatives or its salts, whitening agents including vitamin C, ascorbic acid phosphate magnesium, ascorbyl glucoside, arbutin and kojic acid, and sugars including glucose, fructose, mannose, sucrose and trehalose can also be added.

[0034] The endermic liniment of the present invention can be in any form which is conventionally used as an endermic liniment, including ointment, cream, emulsion, lotion, facial packs and bath additives.

EXAMPLES

[0035] The present invention is described in detail below by referring to examples. The present invention is not limited

to these examples. The blend ratios are in weight percent units. Before explaining the examples, the testing methods and the results of the melanin suppression effect, tyrosinase activity inhibition effect and whitening effect of the plant extract of the present invention are described.

The testing methods and results

1. Sample preparation

[0036] 100 g of the root part of jurubeba paiz was immersed in ethanol at room temperature for a week. The extract solution was then concentrated to obtain 1.6 g of an ethanol extract. This extract was dissolved in DMSO to obtain a 1% solution, and this solution was diluted to adjust the concentration for the following experiments.

[0037] Also, 100 g of the branch part of Cocohuite (scientific name: Gliricidia sepium) was immersed in ethanol at room temperature for a week. The extract solution was then concentrated to obtain 1.9 g of an ethanol extract. This extract was dissolved in DMSO to obtain a 1% solution, and this solution was diluted to adjust the concentration for the following experiments.

[0038] Furthermore, 100 g of the whole plant of Hamula (scientific name: Brickellia cavanillesy) was immersed in ethanol at room temperature for a week. The extract solution was then concentrated to obtain 2.1 g of an ethanol extract. This extract was dissolved in DMSO to obtain a 1% solution, and this solution was diluted to adjust the concentration for the following experiments.

2. Cell culture

[0039] B16 melanoma culture cells from mice were used. A culture was conducted in a CO_2 incubator (95% air and 5% carbon oxide) at 37°C using Eagle's medium containing 10% FBS and theophylline (0.09 mg/ml). After 24 hours of culturing, the sample solution was added to it such that the final concentration (in dried extract) was 10^{-2} - 10^{-5} wt% for jurubeba paiz and 10^{-2} - 10^{-4} wt% for Cocohuite and Hamula. The culture was continued for 3 more days, following which time melanin production was visually evaluated and the tyrosinase activity inihibition effect was measured.

3. Visual evaluation of the amount of melanin

[0040] A diffusion plate was placed on top of the lid of the well plate, and the amount of melanin in the cells was evaluated using an inverted microscope. The evaluation was compared with that of a sample with no added extract from the plant of the Solanaceae family (control sample). The results are shown in Table 1.

[0041] For a reference, the same testing was conducted on Nepeta japonica (Lamium album subfamily, perilla family) extract which was already known to suppress melanin production. These results are also shown in Table 1.

〈Criteria〉

[0042]

○: Whiter than the control (the amount of melanin is less than that in the control)
△ : Somewhat whiter (the amount of melanin is somewhat less than that in the control)
X: Comparable degree of whiteness as the control.

4. Tyrosinase activity measurement

[0043] Before the measurement, the medium in the well(s) was removed, followed by washing twice with 100 microliters of PBS. 45 microliters of PBS containing 1% Triton X (surfactant from Rohm & Haas) was then added to each well. The plate was vibrated for 1 minute to thoroughly destroy the cell membranes, and the absorbance at 475 nm was measured using a microplate reader, which was defined as the absorbance at time 0 minutes. Quickly after this, 5 microliters of 10 mM L-DOPA solution was added and the plate was transferred to an incubator kept at 37°C to react for 60 minutes. The plate was vibrated for 1 minute and the absorbance (475 nm) at time 60 minutes was measured. The tyrosinase activity ratio (%) was defined as a ratio of the absorbance difference between time 0 minutes and time 60 minutes for the sample to which the plant extract was added and the absorbance difference between time 0 minutes and time 60 minutes for the sample to which the plant extract was not added. The results are shown in Table 1.

[0044] For a reference, the same testing was conducted on Nepeta japonica extract which was already known to inhibit tyrosinase activity. These results are also shown in Table 1. In the table, "-" indicates that no significant difference compared with the control was observed within a 5% level of significance. Empty columns indicate that testing was not

conducted for those because the tyrosinase activity inhibition effect had been observed with a lower concentration.

Table 1

Test	Visual evaluation of melanin production				Tyrosinase activity ratio (%)			
Concentration (wt%)	10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-5}	10^{-4}	10^{-3}	10^{-2}
Jurubeba paiz extract	×	○			90	106		
Nepeta japonica extract	×	×	×	×	–	–	–	55
Test —	Visual evaluation of melanin production				Tyrosinase activity ratio (%)			
Concentration (wt%)	10^{-4}	10^{-3}	10^{-2}		10^{-4}	10^{-3}	10^{-2}	
Cocohuite extract	×	○	○		92	73	0	
Nepeta japonica extract	×	×	×		–	–	55	
Test	Visual evaluation of melanin production				Tyrosinase activity ratio (%)			
Concentration (wt%)	10^{-4}	10^{-3}	10^{-2}		10^{-4}	10^{-3}	10^{-2}	
Hamula extract	×	○	○		76	0	0	
Nepeta japonica extract	×	×	×		–	–	55	

5. Whitening effect testing

[Test method]

[0045] 40 testees were exposed to artificial light (UV-A + UV-B) for 30 minutes (10 minutes a day for 3 days) and the skin of an inner lateral part of their upper arm was used as the subject of the test. Beginning after 5 days from the day they were exposed to the sunlight, each sample was applied to this skin once in the morning and once in the afternoon for 4 weeks. The panel was divided into 5 groups with 8 persons in each group. Testing was conducted using the following formulations.

(Alcohol phase)	
95% ethyl alcohol	55.0 wt%
Polyoxyethylene (25-mole) hardened castor oil ether	2.0
Antioxidant/preservative	Appropriate amount
Perfume	Appropriate amount
Drug (specified in Table 2)	
(Water Phase)	
Glycerine	5.0
Sodium hexamethaphosphate	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0046] The water phase and the alcohol phase were prepared separately and then mixed and solubilized.

[Evaluation method]

[0047] The hypochromic effect after the application was evaluated based on the criteria below.

〈Criteria〉

[0048]

◎ : Very effective or effective on 80% or more of the testees
○ : Very effective or effective on 50% to less than 80% of the testees
△ : Very effective or effective on 30% to less than 50% testees
X: Very effective or effective on less than 30% of the testees

[0049] Samples were prepared with the blend compositions described in the aforementioned test method, and the drugs listed in Table 2 were used to compare the whitening effect. The results are shown in Table 2.

Table 2

Drug	Blend ratio (wt%)	Effect
Nothing added	-	X
Hydroquinone	1.0	△
Jurubeba paiz extract	0.1	○
Jurubeba paiz extract	1.0	○
Jurubeba paiz extract	5.0	◎
Cocohuite extract	0.1	○
Cocohuite extract	1.0	○
Cocohuite extract	5.0	◎
Hamula extract	0.1	○
Hamula extract	1.0	○
Hamula extract	5.0	◎

[0050] The jurubeba paiz extracts in Table 2 were obtained by heated reduction of the root of jurubeba paiz in ethanol, followed by filtering and concentration/drying.

[0051] The Cocohuite extracts were obtained by heated reduction of the branches of Cocohuite in ethanol, followed by filtering and concentration/drying.

[0052] The Hamula extracts were obtained by heated reduction of the whole plant of Hamula in ethanol, followed by filtering and concentration/drying.

[0053] As clearly shown in Table 2, it was confirmed that the samples with Jurubeba paiz extract, Cocohuite extract or Hamula extract more effectively prevented excessive deposition of the melanin pigment and thus prevented darkening of the skin.

[0054] Examples of the whitening endermic liniment of the present invention are shown below.

[0055] In "the whitening endermic liniment containing an extract from a plant of the Solanaceae family, genus Solanum", the jurubeba paiz extract was obtained by heated reduction of the root of jurubeba paiz in each extraction solvent, followed by filtering and concentration/drying.

[0056] In "the whitening endermic liniment containing an extract from a plant of the Fabaceae family, genus Gliricidia", the Cocohuite and Gliricilia extracts were obtained by heated reduction of the branches in extraction solvent, followed by filtering and concentration/drying.

[0057] In "the whitening endermic liniment containing an extract from a plant of the Asteraceae family, genus Brickellia", the Hamula extract was obtained by heated reduction of the whole plant of Hamula in ethanol, followed by filtering and concentration/drying.

(1) "The whitening endermic liniment containing an extract from a plant of the Solanaceae family, genus Solanum"

Example 1 Cream

[0058]

(Recipe)	
Stearic acid	5.0 wt%
Stearyl alcohol	4.0
Isopropyl myristate	18.0
Glycerine monostearic ester	3.0
Propylene glycol	10.0
Jurubeba paiz methanol extract	0.01
Caustic potash	0.2
Preservative	Appropriate amount
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0059] Propylene glycol, the jurubeba paiz extract and caustic potash were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase, and after all of it had been added the temperature was kept at that temperature to allow the mixture to react. Finally, the mixture was homogeneously emulsified by a homogenizer and cooled to 30°C while being thoroughly stirred.

Example 2 Cream

[0060]

(Recipe)	
Stearic acid	2.0 wt%
Stearyl alcohol	7.0
Hydrated lanolin	2.0
Squalane	5.0
2-octyldodecyl alcohol	6.0
Polyoxyethylene (25-mole) cetyl alcohol ether	3.0
Glycerine monostearic ester	2.0
Propylene glycol	5.0
Jurubeba paiz ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0061] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and after pre-emulsification, the mixture was homogeneously emulsified by a homogenizer and cooled to 30 °C while being thoroughly stirred.

Example 3 Cream

[0062]

(Formula)	
Solid paraffin	5.0 wt%
Bees wax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerine monostearic ester Polyoxyethylene (20-mole)	2.0
sorbitan monolauric ester	2.0
Soap powder	0.1
2-ethylhexyl paramethoxycinnamate	1.5
Borax	0.2
Jurubeba paiz acetone extract	0.05
Jurubeba paiz ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0063] Soap powder and borax were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase while stirring was conducted to allow the reaction to occur. When the reaction was complete, the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 4 Lotion

[0064]

(Recipe)	
Stearic acid	2.5 wt%
Cetyl alcohol	1.5
Vaseline	5.0
Liquid paraffin	10.0

(continued)

(Recipe)	
Polyoxyethylene (10-mole) monooleic ester	2.0
Polyethylene glycol 1500	3.0
Triethanol amine	1.0
Carboxyvinyl polymer (Product name: Carbopol 941 from B.F. Goodrich Chemical company)	0.05
Eggplant (scientific name: Solanum melongena) fruit ethyl acetate extract	0.01
Placenta extract	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0065] The carboxyvinyl polymer was dissolved in a small amount of the ion exchange water (A phase). Polyethylene glycol 1500 and triethanol amine were added to and heat-dissolved in the rest of the ion exchange water and the temperature was kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and, after pre-emulsification, the A phase was added and the mixture was homogeneously emulsified by a homogenizer and cooled to 30°C while being thoroughly stirred.

Example 5 Lotion

[0066]

(Recipe)	
Microcrystalline wax	1.0 wt%
Bees wax	2.0
Lanolin	20.0
Liquid paraffin	10.0
Squalane	5.0
Sorbitan sesquioleic ester Polyoxyethylene (20-mole)	4.0
sorbitan monooleic ester	1.0
Propylene glycol Solanum aculeatissimum	7.0
fruit acetone extract	10.0
Kojic acid	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0067] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil

phase was gradually added to the water phase while stirring was conducted, and the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 6 Jelly

[0068]

(Recipe)	
95% ethyl alcohol	10.0 wt%
Dipropylene glycol	15.0
Polyoxyethylene (50-mole) oleyl alcohol ether	2.0
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	1.0
Caustic soda	0.15
L-arginine	0.1
Solanum lyratum fruit 50% ethanol aqueous solution extract	7.0
Sodium 2-hydroxy-4-methoxybenzophenonesulfonate	0.05
Ethylenediamine-tetraacetic acid trisodium dihydrate	0.05
Methyl paraben	0.2
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0069] Carbopol 940 was homogeneously dissolved in the ion exchange water. The Solanum lyratum 50% ethanol aqueous solution extract and polyoxyethylene (50-mole) oleyl alcohol ether were dissolved in 95% ethanol and this mixture was added to the water phase. The other ingredients were then added, and the mixture was neutralized and thickened with caustic soda and L-arginine.

Example 7 Essence

[0070]

(Recipe)	
(A phase)	
Ethyl alcohol (95%)	10.0 wt%
Polyoxyethylene (20-mole) octyl dodecanol	1.0
Pantothenyl ethyl ether	0.1
Jurubeba paiz methanol extract	1.5
Ascorbyl glucoside	1.5
Arbutin	3.0
Methyl paraben	0.15
(B phase)	
Potassium hydroxide	0.1
(C phase)	
Glycerine	5.0
Dipropylene glycol	10.0
Sodium hydrogen sulfite	0.03
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	0.2
Purified water	Balance

(Preparation method)

[0071] The A phase and the C phase were independently dissolved homogeneously, and then the A phase was added to the C phase and solubilized. The B phase was then added, and finally containers were filled.

Example 8 Facial pack

[0072]

(Recipe)	
(A phase)	
Dipropylene glycol	5.0 wt%
Polyoxyethylene (60-mole) hardened castor oil	5.0
(B phase)	
Jurubeba paiz methanol extract	0.01
Olive oil	5.0
Tocopherol acetate	0.2
Ethyl paraben	0.2
Perfume	0.2
(C phase)	
Ascorbyl 2-glucoside	2.0
Polyvinyl alcohol	13.0
(Degree of saponification 90, degree of polymerization 2,000) Ethanol	7.0
Purified water	Balance

(Preparation method)

[0073] The A, B and C phases were independently dissolved homogeneously, and then the B phase was added to the A phase and solubilized. The C phase was then added to this, and finally containers were filled.

Example 9 Solid foundation

[0074]

(Recipe)	
Talc	43.1 wt%
Kaolin	15.0
Sericite	10.0
Zinc flower	7.0
Titanium dioxide	3.8
Yellow iron oxide	2.9
Black iron oxide	0.2
Squalane	8.0
Isostearic acid	4.0
POE sorbitan monooleate	3.0
Isocetyl octate	2.0

(continued)

(Recipe)	
Jurubeba paiz ethanol extract	1.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0075] The powder ingredients, i.e. from talc to black iron oxide, were thoroughly mixed by a blender, and the oil-based ingredients, i.e. from squalene to isocetyl octate, and Jurubeba paiz ethanol extract, the preservative and the perfume were added to this. After a thorough kneading, the product was poured into containers and molded.

Example 10 Emulsified foundation (cream type)

[0076]

(Recipe)	
(Powder portion)	
Titanium dioxide	10.3 wt%
Sericite	5.4
Kaolin	3.0
Yellow iron oxide	0.8
Red iron oxide	0.3
Black iron oxide	0.2
(Oil phase)	
Decamethylpentasiloxane	11.5
Liquid paraffin	4.5
Polyoxyethylene modified dimethylpolysiloxane	4.0
(Water Phase)	
Purified water	50.0
1,3-butylene glycol	4.5
Jurubeba paiz ethanol extract	1.5
Sorbitan sesquioleic ester	3.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0077] After heating and stirring the water phase, the powder portion, thoroughly mixed and crushed, was added to it and the mixture was treated with a homogenizer. The heat-mixed oil phase was then added to this mixture and the resulting mixture was treated with a homogenizer. Finally, the perfume was added while the mixture was stirred and the temperature was lowered to room temperature.

(2) "The whitening endermic liniment containing an extract from a plant of the Fabaceae family, genus Gliricidia"

Example 1 Cream

[0078]

(Recipe)	
Stearic acid	5.0 wt%
Stearyl alcohol	4.0
Isopropyl myristate	18.0
Glycerine monostearic ester	3.0
Propylene glycol	10.0
Cocohuite methanol extract	0.01
Caustic potash	0.2
Preservative	Appropriate amount
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0079] Propylene glycol, the Cocohuite methanol extract and caustic potash were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase, and after all of it had been added the temperature was kept at that temperature to allow the mixture to react. Finally, the mixture was homogeneously emulsified by a homogenizer and cooled to 30 °C while being thoroughly stirred.

Example 2 Cream

[0080]

(Recipe)	
Stearic acid	2.0 wt%
Stearyl alcohol	7.0
Hydrated lanolin	2.0
Squalane	5.0
2-octyldodecyl alcohol Polyoxyethylene (25-mole)	6.0
cetyl alcohol ether	3.0
Glycerine monostearic ester	2.0
Propylene glycol	5.0
Cocohuite ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0081] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and after pre-emulsification, the mixture was homogeneously emulsified by a homogenizer and cooled to 30 °C while being thoroughly stirred.

Example 3 Cream

[0082]

(Formula)	
Solid paraffin	5.0 wt%
Bees wax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerine monostearic ester Polyoxyethylene (20-mole)	2.0
sorbitan monolauric ester	2.0
Soap powder	0.1
2-ethylhexyl paramethoxycinnamate	1.5
Borax	0.2
Cocohuite acetone extract	0.05
Ascorbyl 2-glucoside	2.0
Cocohuite paiz ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0083] Soap powder and borax were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase while stirring was conducted to allow the reaction to occur. When the reaction was complete, the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 4 Lotion

[0084]

(Recipe)	
Stearic acid	2.5 wt%
Cetyl alcohol	1.5
Vaseline	5.0

(continued)

(Recipe)	
Liquid paraffin	10.0
Polyoxyethylene (10-mole) monooleic ester	2.0
Polyethylene glycol 1500	3.0
Triethanol amine	1.0
Carboxyvinyl polymer (Product name: Carbopol 941 from B.F. Goodrich Chemical company)	0.05
Gliricia 30% ethanol extract	1.5
Placenta extract	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0085] The carboxyvinyl polymer was dissolved in a small amount of the ion exchange water (A phase). Polyethylene glycol 1500 and triethanol amine were added to and heat-dissolved in the rest of the ion exchange water and the temperature was kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and, after pre-emulsification, the A phase was added and the mixture was homogeneously emulsified by a homogenizer and cooled to 30°C while being thoroughly stirred.

Example 5 Lotion

[0086]

(Recipe)	
Microcrystalline wax	1.0 wt%
Bees wax	2.0
Lanolin	20.0
Liquid paraffin	10.0
Squalane	5.0
Sorbitan sesquioleic ester Polyoxyethylene (20-mole)	4.0
sorbitan monooleic ester	1.0
Propylene glycol	7.0
Cocohuite acetone extract	5.0
Kojic acid	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0087] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water

phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase while stirring was conducted, and the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 6 Jelly

[0088]

(Recipe)	
95% ethyl alcohol	10.0 wt%
Dipropylene glycol	15.0
Polyoxyethylene (50-mole) oleyl alcohol ether	2.0
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	1.0
Caustic soda	0.15
L-arginine	0.1
Cocohuite 50% ethanol aqueous solution extract	1.5
Sodium 2-hydroxy-4-methoxybenzophenonesulfonate	0.05
Ethylenediamine-tetraacetic acid trisodium dihydrate	0.05
Methyl paraben	0.2
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0089] Carbopol 940 was homogeneously dissolved in the ion exchange water. The Cocohuite 50% ethanol aqueous solution extract and polyoxyethylene (50-mole) oleyl alcohol ether were dissolved in 95% ethanol and this mixture was added to the water phase. The other ingredients were then added, and the mixture was neutralized and thickened with caustic soda and L-arginine.

Example 7 Essence

[0090]

(Recipe)	
(A phase)	
Ethyl alcohol (95%)	10.0 wt%
Polyoxyethylene (20-mole) octyl dodecanol	1.0
Pantothenyl ethyl ether	0.1
Cocohuite methanol extract	1.5
Ascorbyl glucoside	1.5
Arbutin	3.0
Methyl paraben	0.15
(B phase)	
Potassium hydroxide	0.1
(C phase)	
Glycerine	5.0
Dipropylene glycol	10.0
Sodium hydrogen sulfite	0.03
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	0.2
Purified water	Balance

(Preparation method)

[0091] The A phase and the C phase were independently dissolved homogeneously, and then the A phase was added to the C phase and solubilized. The B phase was then added, and finally containers were filled.

Example 8 Facial pack

[0092]

(Recipe)	
(A phase)	
Dipropylene glycol	5.0 wt%
Polyoxyethylene (60-mole) hardened castor oil	5.0
(B phase)	
Cocohuite methanol extract	0.01
Olive oil	5.0
Tocopherol acetate	0.2
Ethyl paraben	0.2
Perfume	0.2
(C phase)	
Ascorbyl 2-glucoside	2.0
Polyvinyl alcohol (Degree of saponification 90, degree of polymerization 2,000)	13.0
Ethanol	7.0
Purified water	Balance

(Preparation method)

[0093] The A, B and C phases were independently dissolved homogeneously, and then the B phase was added to the A phase and solubilized. The C phase was then added to this, and finally containers were filled.

Example 9 Solid foundation

[0094]

(Recipe)	
Talc	43.1 wt%
Kaolin	15.0
Sericite	10.0
Zinc flower	7.0
Titanium dioxide	3.8
Yellow iron oxide	2.9
Black iron oxide	0.2
Squalane	8.0
Isostearic acid	4.0
POE sorbitan monooleate	3.0
Isocetyl octate	2.0

(continued)

(Recipe)	
Cocohuite ethanol extract	1.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0095] The powder ingredients, i.e. from talc to black iron oxide, were thoroughly mixed by a blender, and the oil-based ingredients, i.e. from squalene to isocetyl octate, and Cocohuite ethanol extract, the preservative and the perfume were added to this. After a thorough kneading, the product was poured into containers and molded.

Example 10 Emulsified foundation (cream type)

[0096]

(Recipe)	
(Powder portion)	
Titanium dioxide	10.3 wt%
Sericite	5.4
Kaolin	3.0
Yellow iron oxide	0.8
Red iron oxide	0.3
Black iron oxide	0.2
(Oil phase)	
Decamethylpentasiloxane	11.5
Liquid paraffin	4.5
Polyoxyethylene modified dimethylpolysiloxane	4.0
(Water Phase)	
Purified water	50.0
1,3-butylene glycol	4.5
Cocohuite ethanol extract	1.5
Sorbitan sesquioleic ester	3.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0097] After heating and stirring the water phase, the powder portion, thoroughly mixed and crushed, was added to it and the mixture was treated with a homogenizer. The heat-mixed oil phase was then added to this mixture and the resulting mixture was treated with a homogenizer. Finally, the perfume was added while the mixture was stirred and the temperature was lowered to room temperature.

(3) "The whitening endermic liniment containing an extract from a plant of the Asteraceae family, genus Brickellia"

Example 1 Cream

[0098]

(Recipe)	
Stearic acid	5.0 wt%
Stearyl alcohol	4.0
Isopropyl myristate	18.0
Glycerine monostearic ester	3.0
Propylene glycol	10.0
Hamula methanol extract	0.01
Caustic potash	0.2
Preservative	Appropriate amount
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0099] Propylene glycol, the Hamula methanol extract and caustic potash were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase, and after all of it had been added the temperature was kept at that temperature to allow the mixture to react. Finally, the mixture was homogeneously emulsified by a homogenizer and cooled to 30°C while being thoroughly stirred.

Example 2 Cream

[0100]

(Recipe)	
Stearic acid	2.0 wt%
Stearyl alcohol	7.0
Hydrated lanolin	2.0
Squalane	5.0
2-octyldodecyl alcohol	6.0
Polyoxyethylene (25-mole) cetyl alcohol ether	3.0
Glycerine monostearic ester	2.0
Propylene glycol	5.0
Earleaf brickellbush ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0101] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and after pre-emulsification, the mixture was homogeneously emulsified by a homogenizer and cooled to 30 °C while being thoroughly stirred.

Example 3 Cream

[0102]

(Formula)	
Solid paraffin	5.0 wt%
Bees wax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerine monostearic ester	2.0
Polyoxyethylene (20-mole) sorbitan monolauric ester	2.0
Soap powder	0.1
2-ethylhexyl paramethoxycinnamate	1.5
Borax	0.2
Hamula acetone extract	0.05
Ascorbyl 2-glucoside	2.0
Cocohuite paiz ethanol extract	0.05
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0103] Soap powder and borax were added to the ion exchange water and the mixture was heated to and kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase while stirring was conducted to allow the reaction to occur. When the reaction was complete, the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 4 Lotion

[0104]

(Recipe)	
Stearic acid	2.5 wt%
Cetyl alcohol	1.5
Vaseline	5.0

(continued)

(Recipe)	
Liquid paraffin	10.0
Polyoxyethylene (10-mole) monooleic ester	2.0
Polyethylene glycol 1500	3.0
Triethanol amine	1.0
Carboxyvinyl polymer (Product name: Carbopol 941 from B.F. Goodrich Chemical company)	0.05
Hamula 30% ethanol extract	1.5
Placenta extract	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0105] The carboxyvinyl polymer was dissolved in a small amount of the ion exchange water (A phase). Polyethylene glycol 1500 and triethanol amine were added to and heat-dissolved in the rest of the ion exchange water and the temperature was kept at 70°C (water phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was added to the water phase, and, after pre-emulsification, the A phase was added and the mixture was homogeneously emulsified by a homogenizer and cooled to 30°C while being thoroughly stirred.

Example 5 Lotion

[0106]

(Recipe)	
Microcrystalline wax	1.0 wt%
Bees wax	2.0
Lanolin	20.0
Liquid paraffin	10.0
Squalane	5.0
Sorbitan sesquioleic ester	4.0
Polyoxyethylene (20-mole) sorbitan monooleic ester	1.0
Propylene glycol	7.0
Hamula acetone extract	5.0
Kojic acid	1.0
Ethyl paraben	0.3
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0107] Propylene glycol was added to the ion exchange water and the mixture was heated to and kept at 70°C (water

phase). The other ingredients were mixed, then heat-melted and the temperature was kept at 70°C (oil phase). The oil phase was gradually added to the water phase while stirring was conducted, and the mixture was homogeneously emulsified by a homogenizer and then cooled to 30°C while being thoroughly stirred.

Example 6 Jelly

[0108]

(Recipe)	
95% ethyl alcohol	10.0 wt%
Dipropylene glycol	15.0
Polyoxyethylene (50-mole) oleyl alcohol ether	2.0
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	1.0
Caustic soda	0.15
L-arginine	0.1
Betonyleaf brickellbush 50% ethanol extract	1.5
Sodium 2-hydroxy-4-methoxybenzophenonesulfonate	0.05
Ethylenediamine-tetraacetic acid trisodium dihydrate	0.05
Methyl paraben	0.2
Perfume	Appropriate amount
Ion exchange water	Balance

(Preparation method)

[0109] Carbopol 940 was homogeneously dissolved in the ion exchange water. The Betonyleaf brickellbush 50% ethanol aqueous solution extract and polyoxyethylene (50-mole) oleyl alcohol ether were dissolved in 95% ethanol and this mixture was added to the water phase. The other ingredients were then added, and the mixture was neutralized and thickened with caustic soda and L-arginine.

Example 7 Essence

[0110]

(Recipe)	
(A phase)	
Ethyl alcohol (95%)	10.0 wt%
Polyoxyethylene (20-mole) octyl dodecanol	1.0
Pantothenyl ethyl ether	0.1
Hamula methanol extract	1.5
ascorbyl glucoside	1.5
Arbutin	3.0
Methyl paraben	0.15
(B phase)	
Potassium hydroxide	0.1
(C phase)	
Glycerine	5.0
Dipropylene glycol	10.0
Sodium hydrogen sulfite	0.03
Carboxyvinyl polymer (Product name: Carbopol 940 from B.F. Goodrich Chemical company)	0.2
Purified water	Balance

(Preparation method)

[0111] The A phase and the C phase were independently dissolved homogeneously, and then the A phase was added to the C phase and solubilized. The B phase was then added, and finally containers were filled.

Example 8 Facial pack

[0112]

(Recipe)	
(A phase)	
Dipropylene glycol Polyoxyethylene (60-mole)	5.0 wt%
hardened castor oil	5.0
(B phase)	
Hamula methanol extract	0.01
Olive oil	5.0
Tocopherol acetate	0.2
Ethyl paraben	0.2
Perfume	0.2
(C phase)	
Ascorbyl 2-glucoside	2.0
Polyvinyl alcohol (Degree of saponification 90, degree of polymerization 2,000)	13.0
Ethanol	7.0
Purified water	Balance

(Preparation method)

[0113] The A, B and C phases were independently dissolved homogeneously, and then the B phase was added to the A phase and solubilized. The C phase was then added to this, and finally containers were filled.

Example 9 Solid foundation

[0114]

(Recipe)	
Talc	43.1 wt%
Kaolin	15.0
Sericite	10.0
Zinc flower	7.0
Titanium dioxide	3.8
Yellow iron oxide	2.9
Black iron oxide	0.2
Squalane	8.0
Isostearic acid	4.0
POE sorbitan monooleate	3.0
Isocetyl octate	2.0

(continued)

(Recipe)	
Hamula ethanol extract	1.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0115] The powder ingredients, i.e. from talc to black iron oxide, were thoroughly mixed by a blender, and the oil-based ingredients, i.e. from squalene to isocetyl octate, and Hamula ethanol extract, the preservative and the perfume were added to this. After a thorough kneading, the product was poured into containers and molded.

Example 10 Emulsified foundation (cream type)

[0116]

(Recipe)	
(Powder portion)	
Titanium dioxide	10.3 wt%
Sericite	5.4
Kaolin	3.0
Yellow iron oxide	0.8
Red iron oxide	0.3
Black iron oxide	0.2
(Oil phase)	
Decamethylpentasiloxane	11.5
Liquid paraffin	4.5
Polyoxyethylene modified dimethylpolysiloxane	4.0
(Water Phase)	
Purified water	50.0
1,3-butylene glycol	4.5
Hamula ethanol extract	1.5
Sorbitan sesquioleic ester	3.0
Preservative	Appropriate amount
Perfume	Appropriate amount

(Preparation method)

[0117] After heating and stirring the water phase, the powder portion, thoroughly mixed and crushed, was added to it and the mixture was treated with a homogenizer. The heat-mixed oil phase was then added to this mixture and the resulting mixture was treated with a homogenizer. Finally, the perfume was added while the mixture was stirred and the temperature was lowered to room temperature.

INDUSTRIAL APPLICABILITY OF THE INVENTION

[0118] As described thus far, the whitening endermic liniment of the present invention has a melanin production suppression action and a tyrosinase activity suppression action and therefore exhibits superior hypochromic effects and whitening effects on pigment deposition, chloasma, freckles, liver spots, etc. after sun exposure. This endermic liniment is also superior in terms of safety.

Claims

1. A whitening endermic liniment which characteristically contains an extract from a plant of the Solanaceae family, genus Solanum.

2. The whitening endermic liniment of claim 1 wherein the plant of the Solanaceae family, genus Solanum, is jurubeba paiz (scientific name: Solanum paniculatum).

3. The whitening endermic liniment of claim 1 or 2 wherein the blend ratio of the extract from the plant of the Solanaceae family, genus Solanum, is 0.0005 - 10.0 wt%.

4. A whitening endermic liniment which characteristically contains an extract from a plant of the Fabaceae family, genus Gliricidia.

5. The whitening endermic liniment of claim 4 wherein the plant of the Fabaceae family, genus Gliricidia, is Cocohuite (scientific name: Gliricidia sepium).

6. The whitening endermic liniment of claim 4 or 5 wherein the blend ratio of the extract from the plant of the Fabaceae family, genus Gliricidia, is 0.0005 - 10.0 wt%.

7. A whitening endermic liniment which characteristically contains an extract from a plant of the Asteraceae family, genus Brickellia.

8. The whitening endermic liniment of claim 7 wherein the plant of the Asteraceae family, genus Brickellia, is Hamula (scientific name: Brickellia cavanillesy).

9. The whitening endermic liniment of claim 7 or 8 wherein the blend ratio of the extract from the plant of the Asteraceae family, genus Brickellia, is 0.0005 - 10.0 wt%.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/01095

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K7/00, 48, 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K7/00, 48, 35/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), BIOSIS (DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	JP, 8-12565, A (Shiseido Co., Ltd.), January 16, 1996 (16. 01. 96), Claims (Family: none)	1, 3 2, 4-9
A	JP, 5-345705, A (Nippon Shinyaku Co., Ltd.), December 27, 1993 (27. 12. 93), Claims & BE, 814177, A & PT, 61772, A & DD, 113753, A & NL, 7404924, A & DK, 7401860, A & BR, 7404139, A & FR, 2277820, A & US, 3960839, A & GB, 1465392, A & CA, 1029010, A & CH, 608245, A	1-9
P, X	JP, 9-249578, A (K.K. Yakurigaku Chuo Kenkyusho), September 22, 1997 (22. 09. 97), Claims ; Examples (Family: none)	1, 3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
May 26, 1998 (26. 05. 98)	June 2, 1998 (02. 06. 98)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210(second sheet)(July 1992)